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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/777,526	02/06/2001	Sudhir Agrawal	HYZ-030CPCN3 (47508.518)	8659

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	12

DATE MAILED: 10/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/777,526	Applicant(s) AGRAWAL ET AL.	
	Examiner Terra C. Gibbs	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-11 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-11 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-8 and 12-14 were originally filed with this application. ~~Applicant has renumbered~~ have been renumbered M 10/1/02 Claims 12-14 as claims 9-11. The dependency of renumbered claim 9 has been amended. Claims 1-11 are pending in the instant application.

Information Disclosure Statement

The information disclosure statement filed 05/21/01, in Paper No. 6, fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. Applicant is asked to submit a legible copy of each patent or publication contained within the Information Disclosure Statement.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,591,721. Although the conflicting claims are not identical, they are not patentably distinct from each other because: The method for introducing an intact oligonucleotide into a mammal, the method comprising the step of orally administering a chimeric oligonucleotide, the oligonucleotide comprising about 6 to 50 nucleotides linked via at least one phosphorothioate internucleotide linkage and at least one internucleotide linkage, whereby the oligonucleotide is present in intact form in plasma at least six hours following oral administration, of claims 1-11 of the instant invention, embrace the embodiments of claim 1 of '721, a method for introducing an intact oligonucleotide into a mammal, the method comprising the step of orally administering an oligonucleotide of about 15 to 25 nucleotides linked via phosphorothioate internucleoside linkages between every nucleoside, and further comprising at least two 2'-O-methyl-ribonucleotides at each end, whereby the oligonucleotide is present in intact form in the systemic plasma at least six hours following oral administration (see U.S. Patent No. 5,591,721, claim 1; column 3, lines 29-67; and column 4, lines 1-39); specific embodiments of claims 1-11 of the instant invention overlap with the embodiments of claim 1 of '721 (see U.S. Patent No. 5,591,721, claim 1; column 3, lines 29-67; and column 4, lines 1-39). Furthermore, oligonucleotides of claims 1-11 of the instant invention encompass the oligonucleotides of claim 1 of '721 (see U.S. Patent No. 5,591,721, column 4, lines 40-63). For example, a chimeric oligonucleotide of claims 1-11 of the instant invention, comprising about 6 to 50 nucleotides linked via at least one phosphorothioate internucleotide linkage and at least one internucleotide linkage; whereby the oligonucleotide is present in intact form in plasma at least six hours following oral

administration, clearly embrace an oligonucleotide of about 15 to 25 nucleotides linked via phosphorothioate internucleoside linkages between every nucleoside, and further comprising at least two 2'-O-methyl-ribonucleotides at each end, whereby the oligonucleotide is present in intact form in the systemic plasma at least six hours following oral administration, of claim 1 of '721 as evidence by the citations above, for example.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for an all-phosphorothioate oligonucleotide having at least 2'-O-methyl ribonucleotides at the 3' and 5' end, does not provide enablement for an oligonucleotide comprising non-phosphodiester internucleotide linkages, or for an oligonucleotide having fewer than two 2'-O-methyl ribonucleotides at each end. The specification as filed does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-7 are drawn a method for introducing an intact oligonucleotide into a mammal, the method comprising the oral administration of a chimeric oligonucleotide, the oligonucleotide comprising about 6 to 50 nucleotides linked via at least one phosphorothioate internucleotide linkage and at least one internucleotide linkage; whereby the oligonucleotide is present in intact

form in plasma at least six hours following oral administration. Claims 8-11 are drawn to a method for introducing an intact oligonucleotide into a mammal, the method comprising the oral administration of a chimeric oligonucleotide, the oligonucleotide comprising about 6 to 50 nucleotides linked via at least one phosphorothioate internucleotide linkage and at least one internucleotide linkage; whereby the oligonucleotide is present in intact form in plasma at least six hours following oral administration; wherein the oligonucleotide is complementary to a gene of a virus, pathogenic organism, or a cellular gene.

The instant invention specification states that successful operation of the claimed invention was obtained with an all-phosphorothioate oligonucleotide having multiple 2'-O-methyl-ribonucleotides at each end (see page 39, lines 21-31, Example 1). Two published scientific articles co-authored by the Applicants, Agrawal et al. (Biochemical Pharmacology, 1995 Vol. 50:571-576) and Zhang et al. (Biochemical Pharmacology, 1995 Vol. 50:545-556) teach that successful operation of the claimed invention was obtained with an all-phosphorothioate oligonucleotide with four 2'-O-methyl-ribonucleotides at each end. No guidance is provided in the specification or in the published literature regarding successful operation of the claimed invention using any type of oligonucleotide other than an all-phosphorothioate oligonucleotide having at least two 2'-O-methyl-ribonucleotides at each end.

Given the lack of guidance in the specification regarding successful operation with any type of oligonucleotide except an all phosphorothioate oligonucleotide having at least two 2'O-methyl ribonucleotides at each end, undue experimentation would have been required by one skilled in the art at the time the application was filed to practice the claimed invention using *any*

type of oligonucleotide claimed, except for an all phosphorothioate oligonucleotide having at least two 2'-O-methyl ribonucleotides at each end.

Additionally, claims 1-11 represent a broad scope because, given their broadest interpretation, they read on treating *any* disease via oral administration of an all phosphorothioate oligonucleotide having at least two 2'-O-methyl ribonucleotides at each end. Methods of targeting oligonucleotides into a subject (whole organism) fall into the broad area known as gene therapy methods. While delivery of nucleic acids in and of itself is not considered as therapy *per se*, delivery shares many of the obstacles recognized for the actual therapy methods because successful therapy methods are, for the most part, based on the ability to deliver exogenous nucleic acids to cells or tissues of interest. Branch (TIBS Vol. 23, February 1998) teaches that the *in vivo* (whole organism) application of nucleic acids is a highly unpredictable endeavor due to target accessibility and delivery issues (see entire text).

It would appear that in view of the above, one of ordinary skill in the art would require specific guidance on how to practice the current invention. The current specification does not provide such guidance and one of ordinary skill in the art would be required to perform undue trail and error experimentation to practice the current invention. The quantity of undue experimentation would include overcoming the obstacle to routine antisense therapy as exemplified in the reference discussed above.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 746-8693.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
October 1, 2002

SEAN McGARRY
PRIMARY EXAMINER
1635